PATENT
Docket No. 381092000720

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Terrance P. SNUTCH, *et al.*

Serial No.: 09/346,794

Filing Date: 02 July 1999

For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

Examiner: Nirmal S. Basi

Group Art Unit: 1646

DECLARATION OF DR. TERRANCE SNUTCH

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Terrance Snutch, declare as follows:

1. I am a co-inventor of the subject matter claimed in the above-referenced application and have been practicing in the field of molecular biology, and specifically in the field of ion channels, for over 15 years. A copy of my *curriculum vitae* is attached hereto as Exhibit A. I have published many papers on the structure and function of calcium channels and am considered one of the leading researchers in this field.

2. The association of abnormal T-type calcium channel activity with specific conditions is well known in the art. Enclosed herewith are a number of documents which verify this. Abnormal T-type activity is associated with a number of cardiac conditions including

pacemaker activity (Hajiwara, *et al., J. Physiol.* (1988) 395:233-253; cardiac hypertrophy (Nuss, *et al., Circ. Res.* (1995) 73:777-782); and hypertension (Self, *et al., J. Vasc. Res.* (1994) 31:359-366). Abnormal T-type calcium function is also associated with neurological diseases wherein neuronal bursts are abnormally fired causing spastic convulsions (Huguenard, *Ann. Rev. Physiol.* (1996) 58:329-348) and thus associated with epilepsy (Tsakiridou, *et al., J. Neuro. Sci.* (1995) 15:3110-3117; Coulter, *et al., Brit. J. Pharmacol.* (1990) 100:800-806). Abnormal function of the T-type calcium ion channel is also associated with impaired fertility because of its effect on hormone secretion (Rossier, *et al., Endocrinology* (1966) 137:4817-4826; Arnoult, *et al., Proc. Natl. Acad. Sci. USA* (1996) 93:13004-13009). Copies of these documents are attached hereto. Thus the conditions associated with abnormal T-calcium channel function are well established and agonists and antagonists of T-type calcium channels are useful in treating these conditions.

3. There are several T-type calcium channels found in a single individual which vary slightly in structure and demonstrably in terms of their distribution among various tissues. This, however, does not affect the usefulness of screening assays for agonists and antagonists. The particular T-type calcium channel involved in a particular condition may depend on its tissue distribution; for instance, T-type channels found in the nervous system are associated with epilepsy and neurological diseases in general where spastic convulsions are involved. However, it is not necessary to understand which particular T-type calcium channel is being used in a screen for compounds that would be useful in treating, for example, these convulsive conditions because of the similarity in the binding specificity of all T-type channels. In very simple terms, compounds which are found to inhibit or stimulate the activity of nervous T-type channels will also inhibit or stimulate the activity of T-type channels found in other tissues. Thus, any arbitrarily chosen T-type channel could be expressed in a cell line for use in screening assays to identify agonists or antagonists and the agonists or antagonists would be useful in treating the conditions associated with any T-type channel. As noted above, abnormal T-type activity is associated with a number of cardiac conditions, with hypertension, with neurological diseases involving spastic convulsions, and with impaired fertility. An agonist or antagonist identified with regard to any T-type channel would be useful in any and all of these conditions.

4. This pattern of similar binding activity among all T-type channels can be analogized to such a pattern among L-type channels. All of the T-type channels have similar

behaviors in that they activate at low membrane potential, have small single channel conductance, have negative steady state inactivation properties, and contribute to spike firing patterns and rhythmic bursting processes. Analogous to the T-type channel another type of channel linked by similar behaviors is the L-type. There are several α_1 subunits associated with various L-type channels - *i.e.*, α_{1S}, α_{1C}, and α_{1D} and each is encoded by a distinct gene and exhibits a distinct distribution pattern. For example, α_{1S} is in skeletal muscle; α_{1C} is in neurons and cardiac and smooth muscle; and α_{1D} is found in neurons and endocrine cells. They can be discriminated from all other types of calcium channels by their common sensitivity to 1,4-dihydropyridines. Thus, any one of these genes could be used to generate an L-type calcium channel for use in a cell-based assay to identify interacting compounds. These interacting compounds bind to all L-type channels and thus are useful in treating conditions related to any one of them.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at VANCOUVER, BC on 10 July 2001.

Terrance Snutch